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EPA Working Group on Amitraz
Environmental Protection Agency

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CONTENTS

Page

I. Background 1
A. Characteristics of Amitraz 1
(1) Nomenclature 1
(2) Chemistry 1
(3) Toxicity 1
(4) Formulation 1
(5) Metabolism 2
B. Registered Uses 2
(1) United States 2
(2) International 3
C. Supply 4
II. Regulatory History 4
A. Past Actions and Recommendations 4
B. Referral to OSPR 5
(1) Source - Registration 5
(2) OSPR Response 5
III. Summary of Scientific Evidence to Support Rebuttable Presumption 5
A. Summary of EPA Findings 6
B. Review of the Boots Mouse Study 7
(1) "80-week Carcinogenicity Study in Mice - Final Report" 7
(a) Methods 7
(b) Results 8
(2) Interpretations of the Boots Study 9
(a) Statistics 9
(b) LR Tumor Etiology 9
(c) Viral Induction of LR Tumors 11
(d) Overall Interpretation of the Findings of the Boots Study 12
IV. Other Effects Related to Oncogenicity 13
A. 2,4,-Dimethylaniline - A Potential Metabolite 13
B. Effects of Amitraz in Rats 14
C. Structurally Related Compounds 14
D. Effects of Amitraz in Dogs 14
E. Mutagenic Effects 14
V. Request for Information 15

List of References 16

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I. BACKGROUND

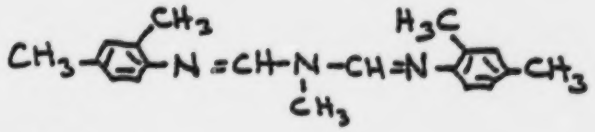
A. Characteristics of Amitraz

(1) Nomenclature

Amitraz is the common name for the chemical N'-(2,4-dimethylphenyl)-N-[[(2,4-dimethylphenyl)imino]methyl]-N-methylmethanimidamide. Experimentally it is known as Triazid, U-36059, BTS 27419, RD 27419, Ent 27967, or JA-119. The formulated product for which registration with EPA is pending is BAAM EC.

(2) Chemistry

Technical grade Amitraz is a white, crystalline solid with a melting point of 86-87 °C. It is soluble in common organic solvents and only slightly soluble in water. The molecular weight is 293, and the molecular formula is $C_{19}H_{23}N_3$. The structural formula is:



(3) Toxicity

The Office of Pesticide Programs (OPP) Registration Division retains toxicity and other data submitted for tolerance petitions. Two of these petitions are described in Section I.B.(1). Some toxicity data for which trade secrecy has been asserted have been examined in the preparation of this document.

An extensive literature search has revealed little published toxicity information. The Farm Chemicals Handbook of 1976 reports: Acute oral LD-50 (rat) = 938 mg/kg; Dermal LD-50 (rabbit) $\geq$ 200 mg/kg; and Acute LD-50 (bees) = 21 mg/bee (Meister 1976).

A Japanese journal reports: Acute oral LD-50 (male mouse) = 1460 mg/kg; 48 hour TLM (young carp) = 1.17 ppm; and Acute oral LD-50 (rat) = 450 mg/kg (Nakamura et al. 1975).

(4) Formulation

The product BAAM is formulated as an emulsifiable concentrate with 19.8% Amitraz as the active ingredient.

(5) Metabolism

The metabolic pathway of Amitraz in mammals has been determined by the Boots Company through extensive tests in dogs, rats, cows, and other animals (Upjohn 1976a). Some of the intermediate products and an end product have been described, thus identifying the probable metabolic pathways of Amitraz through mammals. These identified compounds are:

BTS 27,271 -- (intermediate) -- N-(2,4-dimethylphenyl)-N'-methylformamidine

BTS 27,919 --(intermediate) -- 2,4-dimethylformanilide
BTS 24,868 -- (intermediate) -- 2,4-dimethylaniline
BTS 28,369 -- (end product) -- 4-Amino-3-methylbenzoic acid

B. Registered Uses

(1) United States

There are no registered uses of BAAM in the United States. Only the technical grade material is registered by the Upjohn Company as "Stabilized U-36,059 Technical" under EPA registration number 1023-58.

The Upjohn Company has applied to EPA to use Amitraz as an active ingredient in a product to be called BAAM EC Miticide/Insecticide for Apples and Pears. As required by regulations pursuant to Section 3(c)(1)(D) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), EPA has acknowledged receipt of this application and has placed the proposed label in an open file for public viewing (FR 41, No. 159; August 16, 1976).

As a necessary step in obtaining approval for its application, the Upjohn Company has also submitted two petitions for use of BAAM on food or feed products. A petition is pending for tolerances of 3 ppm on pears; 1 ppm on apples; 0.05 ppm in meat, fat, and meat by-products of cattle, goats, hogs, horses, and sheep; and 0.01 ppm in milk. A food additive petition is also pending for 10 ppm on dried apple pomace. No interim or permanent tolerances have been established. However, temporary tolerances have been established for the duration of an experimental use permit (on apples and pears) which expires April 5, 1977. A request for extension of this permit has been received from Upjohn and is under consideration.

(2) International

There are 25 other countries in which Amitraz is registered as an insecticide, miticide, or acaricide. Table 1 provides a summary (Letter 1977a).

Table 1 - Crop Protection and Animal Health Registrations - December, 1976.

Argentina	apples
Australia	apples
Bulgaria	apples
Chile	fruit and vegetables
Czechoslovakia	top fruit and hops
Denmark	top fruit
Greece	top fruit and vegetables
Hungary	top fruit and vines
*Italy	fruit and vegetables
Japan	top fruit and citrus
The Netherlands	top fruit
Nicaragua	cotton
Peru	cotton
South Africa	apples
South Korea	top fruit and citrus
Spain	top fruit, citrus, vegetables
Switzerland	top fruit
Taiwan	top fruit and citrus
Turkey	cotton, top fruit, citrus
U.K.	top fruit
Argentina	sheep
Australia	cattle
Brazil	cattle
Colombia	cattle
Jamaica	cattle
Rhodesia	cattle
South Africa	cattle
*U.K.	pigs
Venezuela	cattle

(*unofficial)

In Great Britain, Amitraz is formulated and sold by the Boots Company, Ltd. as Mitac 20 under a provisional clearance (i.e., 1-year registration) for apples and pears. First granted in 1976, this clearance has been extended through 1977. A limited clearance, the equivalent of an EPA experimental use permit, is in effect for strawberries, hops, black currants, and plums on a limited acreage.

C. Supply

There are no manufacturers of Amitraz in the United States. However, the Tuco Division of the Upjohn Chemical Company (Kalamazoo, Michigan) has applied for the registration of BAAM EC in order to import Amitraz from the Boots Company, Ltd. Upjohn would then formulate and distribute BAAM EC for commercial use. BAAM EC would probably replace the market for chlordimeform (Galecron and Fundal), for mitigating pear psylla in Oregon, Washington, and California.

II. REGULATORY HISTORY

A. Past Actions and Recommendations

On October 7, 1974, the Upjohn Company submitted a petition for residue tolerances for Amitraz and its metabolites on apples and pears at 0.5 ppm. EPA filed (accepted) the petition on October 25, 1974. Upjohn requested that this petition be amended to 1.0 ppm tolerance on apples and pears on January 20, 1975.

On February 13, 1975, a temporary tolerance was approved for the duration of experimental use of BAAM EC under permit #1023-EUP-34 on apples and pears (February 26, 1975 to February 28, 1976).

On April 10, 1975, technical grade (93%) Amitraz was registered. On April 22, 1975, Upjohn submitted a petition for tolerance for Amitraz and its metabolites on grapefruit, lemons, oranges, tangerines, and tangelos at 1 ppm; in meat, fat, and meat byproducts of cattle, goats, hogs, horses, and sheep at 0.05 ppm; and in milk at 0.01 ppm. Upjohn also submitted a food additive petition for citrus pulp at 3 ppm. EPA filed both petitions on June 5, 1975.

On September 2, 1975, a one-year experimental use permit (#1023-EUP-35) was approved for use of BAAM EC on citrus. Upjohn submitted a request for extension of this permit on July 7, 1976. The permit expired on September 2, [illegible].

Use of BAAM 50W on apples and pears until April 5, 1977, was approved on April 5, 1976, under an experimental use permit.

On June 22, 1976, Upjohn submitted a pesticide petition and food additive petition, as described in Section I.B.(1). On July 23, 1976, Upjohn submitted its application for registration of BAAM EC. On August 30, 1976, after reviewing Upjohn's pesticide petition, EPA's Registration

Division Toxicology Branch concluded that Amitraz caused a significant increase in the incidence of lymphoreticular tumors in female mice fed 400 ppm for 80 weeks, and recommended denial of the tolerance.

B. Referral to OSPR

(1) Source - Registration Division

On the basis of the Toxicology Branch conclusions of August 30, 1976, Dr. Martin H. Rogoff, Associate Director for Scientific Review of the Registration Division, referred BAAM to OSPR on October 15, 1976, for RPAR review of Boots' mouse carcinogenesis study (Burnett et al. 1976; Memo 1976g)

Dr. Rogoff recommended on November 18, 1976, that RPAR review be suspended until the Toxicology Branch had reviewed a report from Upjohn Company which raised questions as to the validity of the 80-week mouse carcinogenesis study it submitted to EPA (Memo 1976f)

A memo from Dr. Rogoff on December 2, 1976, recommended that the RPAR review continue since the Toxicology Branch had completed its review of Upjohn's supplemental report and had maintained its original conclusion of August 30, 1976 (Memo 1976b).

(2) OSPR Response

On December 15, 1976, OSPR formed a working group of representatives of offices throughout EPA to conduct the inquiry into the Boots carcinogenesis study and into any other available information relevant to potential oncogenic effects of Amitraz. The Working Group has sought and received reports from contracted consultants (hereafter called EPA consultants) and from EPA's Carcinogen Assessment Group (CAG). The Working Group has independently reviewed these reports and those submitted by the Boots Company and the Upjohn Company. A summary of the Working Group's conclusions is contained in Section III.A.

III. SUMMARY OF SCIENTIFIC EVIDENCE TO SUPPORT REBUTTABLE PRESUMPTION

40 CFR Section 162.11(a)(3)(ii)(A) provides that "a rebuttable presumption shall arise if a pesticide's ingredient(s) . . . (i)nduces oncogenic effects in experimental mammalian species or in man as a result of oral, inhalation, or dermal exposure . . . ." Section 162.3(bb) defines the

term oncogenic as "the property of a substance or a mixture of substances to produce or induce benign or malignant tumor formation in living animals."

This oncogenic trigger for issuance of an RPAR is the only one which the Working Group has been able to examine. However, the Working Group will continue its evaluation of this and other RPAR criteria. OPP will also be reviewing test data to determine whether relevant non-oncogenic risk criteria have been exceeded. Should additional evidence indicate that the other risk criteria have been exceeded, this position document will be redrafted and a notice will be published in the Federal Register. The pesticide producer is put on notice of his obligation to satisfy all of the risk criteria (40 CFR 162.11(a)). Until all the risk criteria have been fully evaluated, the pesticide cannot be registered. If the oncogenicity risk criterion is successfully rebutted before all the other risk criteria are evaluated, the agency may be required to issue one or more additional RPAR notices should additional risk criteria be exceeded by Amitraz (BAAM). In this situation all Amitraz (BAAM) data gathered by the Agency would be relevant to the Agency's risk/benefit assessment of this pesticide.

At this time, the only scientific evidence available which, by itself, meets the criterion for oncogenicity is the Boots Chemical Company study entitled "BTS 27419: 80-week Carcinogenesis Study in Mice -- Final Report" (Burnett et al. 1976).

Section A, below, contains the findings of EPA as to the evidence in this study which meets the criterion for oncogenic effects cited above. Section B presents methods and results of the Boots' report. Interpretations of the reports by Boots and Upjohn are presented, then compared and contrasted with those of CAG, EPA consultants, and the Working Group. Section C contains an EPA request for information which would help clarify the oncogenicity of Amitraz and BAAM.

A. Summary of EPA Findings

1. The dose-response relationship for lymphoreticular (LR) tumors in female mice shows a significantly increasing linear trend ($p<.02$).

2. The incidences of LR tumors in the high dose (400 ppm) and control (0 ppm) female mice are 0.49 and 0.23, respectively, and are significantly different from each other at ($p<.03$).

3. The dose-response relationship for lung lesions

in female mice, whose sample sizes were corrected for survival, shows a significantly increasing linear trend ($p<.05$).

4. No satisfactory explanation has been presented to account for these relationships other than the oncogenic activity of Amitraz. Thus Amitraz and BAAM, its formulated product, meet the criterion for oncogenic effects.

B. Review of the Boots Mouse Study

(1) "80-week Carcinogenicity Study in Mice - Final Report" (Burnett et al. 1976)

(a) Methods

CAG has summarized the experimental methods employed by Boots as follows (EPA 1977):

"CFLP mice (Anglia Laboratories (Carworth)) mice were used in the study. It is an outbred strain not available in the U.S. which was originally derived from the albino Swiss Schofield strain at Imperial Chemical Industries in the 1950's. Since then it was rederived by fostering pups on gnotobiotic CFL mice.

"Male and female mice were received at 21-23 days; after 2 weeks acclimatization, they were divided into groups of 5 animals/cage. Cages were mounted in a rectangular array on the wall in fixed position throughout the study; the 10 cages of sex/treatment group were in a row. The cage height on the wall was different for each of the 4 treatment groups and in decreasing order was control, lowest-, middle-, and highest-dosage BAAM groups; the sexes were separated.

"In most cases same-sex littermates were put into different treatment groups; 2 or more siblings seldom were put into the same treatment group unless the other three treatment groups contained a member of that litter. Littermates were never allocated to the same cage. Very frequently littermates were placed in cages on the wall that were in the same or adjacent column of cages.

"Animals received powdered Oxoid breeding diet for 2 weeks. BAAM was then added at 0, 25, 100 and 400 ppm and fed for 80-84 wks. Diets were prepared weekly.

"Extra animals, fed identically to those in the original treatment groups were used to replace mice

which died or became unthrifty during the first 12 weeks of the study.

"After 80 weeks feeding, surviving animals were sacrificed over a 4-week period and examined. Animals dying during the study were handled similarly, when possible. Histopathological examination was not possible on 18 males and 22 females due to autolysis or cannibalism. Animals were observed for clinical signs at least weekly throughout the study. A blood smear was taken from each animal and gross examination of organs and cavities was performed.

"Thymus was rarely fixed and examined, and lymph nodes were taken from most but not all animals."

(b) Results

The results of the Boots study were as follows.

1. Lymphoreticular tumor incidences showed dose-related increases. They were 0.23, 0.32, 0.34 and 0.49, respectively, in control, low-, middle-, and high-dosage Amitraz-treated female mice.

2. Lesions of the lung (hyperplasia, adenomas, and carcinomas) in female mice whose sample sizes were corrected for survival were 0.26, 0.48, 0.34, and 0.55, respectively, in control, low-, middle-, and high-dosage Amitraz-fed groups.

3. The incidence of all types of liver tumors was higher in five of six Amitraz treatment groups in both males and females than in the controls.

4. Estimated food consumption was greater among high-dose (400 ppm) males than among males in the other dosage groups; females had a greater intake than males throughout the test; and the high-dose (400 ppm) females tended to show greater consumption than the controls (0 ppm), while the low (25 ppm) and medium (100 ppm) females ate less than the controls.

5. Body-weight gain in the high-dose males was 37% less than the control group at the first 40 weeks, but only 16% less at 80 weeks; female body-weights were less adversely affected than males; high-dose females had 18% less body-weight gain than controls at 40 weeks, and only 9% less at 80 weeks.

(2) Interpretations of the Boots Study

In interpreting this study, its authors, the Boots consultants, and the Upjohn Company raise four particular issues: (a) the statistics of the tumor incidences, (b) the possibility that the LR tumors arose as a non-specific response to several factors in combination with Amitraz, (c) the potential for viral induction of LR tumors, and (d) the overall interpretation of the results.

(a) Statistics

The results of the Boots study are stated and discussed in Section III.B.(1)(b). To provide a quantitative basis for an interpretation of the mouse tumor data, the authors of the Boots study conducted various statistical comparisons. They concluded that the only pathological finding of note was the significantly higher incidence of LR tumors in high-dosage females as compared to that in the controls (Burnett et al. 1976). Later, both a Boots' consultant and the Upjohn Company expressed their confirmation of this finding (Roe 1976; Letter 1976a; 1977b).

In addition, CAG found that:

1. The LR tumors in female mice exhibit a significantly increasing linear trend in dose-response relationship ($p < .02$);

2. Survival-corrected female mice show a significantly increasing linear trend in the dose-response relationship for lung lesions ($p < .05$) (EPA 1977).

The Working Group finds that these statistical determinations by Boots, Upjohn and the EPA meet the RPAR criterion for oncogenic effects.

(b) LR Tumor Etiology

The primary conclusion presented by the authors of the Boots study was that LR tumors could have been a non-specific response to the combination of several factors and Amitraz. They listed such factors as the mouse strain, endocrinal activity, immunological response and dietary intake.

(i) Mouse Strain

Both a consultant for the Boots Company, Dr. Roe, and

one of the Boots study authors, Dr. Turnbull, have asserted that the genetic background of the mice contributed to the incidence of LR tumors in treated females. Dr. Roe stated that the historical incidence of such tumors in these mice was relatively high compared to other mouse strains, while Dr. Turnbull asserted the background incidence was intermediate to that of other strains (Roe 1976; Turnbull 1976b).

The EPA consultants have commented:

"Swiss albino mice are widespread, outbred, and consequently somewhat variable genetically. The isolation of the CFLP strain is likely to have stabilized its genetic variability somewhat, but without inbreeding it cannot be regarded as a strain with homogeneous characteristics. It is not appropriate to compare its spontaneous incidence of tumors quantitatively with that of other Swiss strains. The most precise information available to the review team is that provided in the Upjohn submission. These tabulate observations in untreated mice in 13 experiments completed between 1972 and 1975. With one exception . . . these experiments appear to have been conducted under similar conditions to that with BAAM, and for the same exposure period, and hence should be directly comparable.

"In males, the incidence of LR tumors in controls varied between 3% and 20%, mean 12%. None of these incidences falls outside the 95% probability limits for a binomial distribution based on a uniform probability of occurrence of 0.12 . . .In females the incidence in controls varied between 10% and 31%, mean 19%. None of these incidences falls outside the 90% probability limits for a binomial distribution based on a uniform probability of occurrence of 0.19. In neither sex do the figures for spontaneous incidence show a significant upward or downward trend with time" (Parks et al. 1977 Report of consultants. Clement Assoc., Inc.).

Generally, then, this analysis shows that the historical incidence of LR tumors in the present Boots study mice falls within the normal range of the incidences in historical studies. Thus, there is insufficient evidence to indicate the LR tumors observed in treated females arose spontaneously.

(ii) Endocrinal Activity and Immune Response

The Boots Company and its consultants suggested that the activity or response of the endocrine or immunological systems of the mice contributed to the induction of the LR tumors. The authors of the Boots study admitted, how-

ever, that it had found no evidence to support these suggestions. The Working Group agrees.

(iii) Food Intake

The Boots study suggests that overfeeding of mice is associated with tumor induction. The authors state that the female mice ate more food per bodyweight than did males; so they concluded that it was likely that food intake accounted for the increase in tumors.

The EPA consultants do not agree:

"[Dr.] Roe points out an association between incidence of lymphosarcomas and food intake. However, in our experience . . . the association is between tumor incidence and condition (body-weight) rather than with food intake per se. In this experiment, the group with the largest tumor incidence was the 400 ppm females, which had an increased food intake but decreased body-weight. In any case, as [Dr.] Roe pointed out, one would have expected the effect to have shown up also in males, in which the effects on food intake and body-weight were proportionately larger" (Parks et al. 1977b).

Consequently, the Working Group finds the food intake argument to be unsupported.

(c) Viral Induction of LR Tumors

The Upjohn Company has asserted that the higher incidence of LR tumors in female mice is the result of a horizontal or vertical spread of a leukemia virus.

To support the hypothesis of a horizontal spread of virus, Upjohn claims that the frequency of tumor-bearing females in the lower right quadrant of cages was significantly higher than the frequency of tumor-bearing females in the lower left quadrant (Kakuk 1976). However, Kakuk did not apply a correction for continuity in his chi-square computation. When the appropriate correction is included, the difference is not significant ($p>.08$). CAG and the EPA consultants also analyzed the possibility of clustering of LR tumors by litter and cage and found no evidence of clustering (Parks et al. 1977; EPA 1977).

Kakuk also discussed vertical spread of a virus by showing that certain litters appeared to be over-represented in the LR tumor group. However, when an analysis was performed by CAG and the EPA consultants there was very good agreement between the number of affected animals observed and those expected, assuming a uniform probability for any animal being affected.

An electron microscope study was initiated to find leukemia virus in the LR tumor tissue of the high dose female mice (Robinson 1976). Tissues from two such mice were examined. While there was some suggestion of viral particles in the examined tissue, the poor condition of the preserved tissue made impossible a certain determination.

On the basis of the analyses of the CAG and the EPA consultants, the Working Group finds no evidence of a vertical or horizontal viral spread.

(d) Overall Interpretation of the Findings in the Boots Study

The Boots' consultants, the Upjohn Company, the EPA consultants, and CAG have offered various interpretations of the Boots mouse report data.

The Boots and Upjohn Companies concluded that the Boots' mouse test results in no way establish that Amitraz caused tumors. The facts they cited in addition to evidence already discussed included (1) the lack of LR tumors in male mice, (2) the lack of change in the latency period or overall incidence of tumors, (3) the apparent negative results for rats, (4) the apparent negative results of several mutagenic assays, (5) the lack of teratogenic effects in rats or rabbits, and (6) a lack of significant differences in mortality among groups (Burnett et al. 1976; Roe 1976; Vesselinovitch 1976; Turnbull 1976b; and Letter 1976a).

On the other hand, the EPA consultants concluded that the Boots' mouse test results constituted "substantial evidence" of carcinogenicity in CFLP mice, although the evidence "fell somewhat short of definitive proof" (Parks et al. 1977b). They also noted that the study was conducted for only 80 weeks, as opposed to the 24 months recommedned by National Cancer Institute guidelines, and concluded that the test was "expected to be insensitive . . . for carcinogenicity." The consultants for EPA also examined the chronic feeding studies for rats and dogs, and assessed the results of the mutagenic assays, but did not report that these studies affected an interpretation of the Boots mouse test results.

CAG also found the mouse study meets the RPAR criterion for oncogenic effects. They stated that this criterion "is a statistically significant excess tumor incidence in a study that cannot be dismissed as invalid" (EPA 1977).

To reach an overall interpretation of the mouse study

in relation to the oncogenic criterion requires an answer to the question, did Amitraz induce any oncogenic effects?

The Boots and the Upjohn companies concluded that the only oncogenic effect was the significantly greater incidence of LR tumor in the female mice, but that this effect was explained away by other evidence. However, the information or explanation proposed by Boots and Upjohn [and discussed in Section III.B.(2)] to refute the Boots data have been found by the CAG or the EPA consultants to be unsubstantiated.

A statistically significant increase in LR tumors in treated female mice cannot be explained away by any of the six facts Boots and Upjohn cite above (lack of LR tumors in mice, lack of change in latency period, etc.). These facts similarly do not refute the dose-response relationships found in both the LR tumors and lung lesions of treated female mice. Therefore, the Working Group finds that the criterion for oncogenic effects has been met.

IV. OTHER EFFECTS RELATED TO ONCOGENICITY

The Working Group examined other oncogenicity-related effects of Amitraz. Individually these studies presented insufficient evidence to initiate a rebuttable presumption on the basis of oncogenic effects.

A. 2,4,-dimethylaniline - A Potential Metabolite

As mentioned in Section I.A.(5), 2,4-dimethylaniline (BTS 24868) may be a metabolite of Amitraz. The Boots Company has traced the fate of Amitraz in dogs' stomachs and identified BTS 24868 as a breakdown product (Upjohn 1976b).

A recent National Cancer Institute study has presented some suggestive evidence that the compound exhibits some oncogenic effects (Homburger et al. 1973). CAG has reviewed this study and found that sarcomas occurred more frequently in treated female mice than in control mice, and treated male rats had a higher incidence of malignancies than did controls (EPA 1977).

B. Effects of Amitraz in Rats

A two-year feeding study by the Boots Company presented evidence that Amitraz is not carcinogenic in rats (Sutton and Offer 1973).

CAG has found no significant differences in tumor rates among treatment groups except for pituitary adenomas. In this case, the ratios of tumor-bearing male rats to the tested populations were 4/40, 9/40, 18/39, and 8/40 in the zero, 15, 50, and 200 ppm Amitraz-treated groups, respectively ($p<.05$). To CAG the significance associated with pituitary adenomas was due to the 50 ppm dosage group. CAG found it doubtful that the finding represented a chemically induced effect. The EPA consultants concurred.

C. Effects of Amitraz in Dogs

The Boots Company has conducted a long-term feeding study of the effects of Amitraz on dogs. Boots observed no tumors in any of the dogs. The EPA consultants evaluated the study results and concurred. They state, however, that the duration of the test was not adequate for it to be considered as a carcinogenic bioassay.

D. Structurally Related Compounds

On September 6, 1976, the Ciba-Geigy and Nor-Am Corporations voluntarily recalled their chlordimeform-containing pesticide products, since preliminary results indicated chlordimeform induced a significant increase of malignant tumors in mice.

In November 1976, the Registration Division of OPP recommended that OSPR review the literature to uncover the potential of the formamidine class compounds, which included chlordimeform and Amitraz, to cause oncogenic effects.

Soon thereafter, Upjohn submitted to EPA a report of the Boots Company on the relationship of Amitraz to chlordimeform. This study stated that there are no metabolites common to the breakdown pathways of these two chemicals and that there are differences in their molecular structures as well. The report concluded that on this basis no connection could be drawn between the toxicological potential of chlordimeform and that of Amitraz.

The EPA consultants have generally concurred (Parks et al. 1977).

E. Mutagenic Effects

The Upjohn Company has submitted to EPA the results of

several mutagenicity tests conducted by the Boots Company. (Everest and Wilcox 1976). These tests were evaluated by Boots as revealing a non-mutagenic response for Amitraz and several of its metabolites, BTS 27271, BTS 27919 and BTS 28369.

The EPA consultants did not validate this mutagenicity report. It lacks detailed description of methods, referring to an outdated paper by Ames and to two unpublished company reports. The studies did not use the more sensitive bacterial strains developed since 1973, used phenobarbitone instead of Aroclor 1254 as an enzyme inducer, and did not use metabolic activation at all for the metabolites. Moreover, the results with positive controls were irregular and lower than those usually obtained in this assay (Parks et al. 1977).

V. REQUEST FOR INFORMATION

In order to more adequately assess the oncogenic potenital of Amitraz, BAAM or their metabolites or degradation products, the EPA requests:

1. Access to the histological slides generated in the Boots mouse and rat carcinogenicity studies;

2. Further information on the metabolites of Amitraz, especially on the status of 2,4-dimethylaniline;

3. Information on the tumor types and rates in control CFLP mice and Ash-Wistar rats from the supplier or animals in the Boot's studies.

The EPA also requests additional information available on other risk criteria listed in 40 CFR 162.11(a)(3), in order to assess any other potential risks of Amitraz.

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